CIAO COVID AOP Early KE harmonization:

SARS-CoV-2 entry and antagonism of Interferon (IFN)-I antiviral response leading to replication

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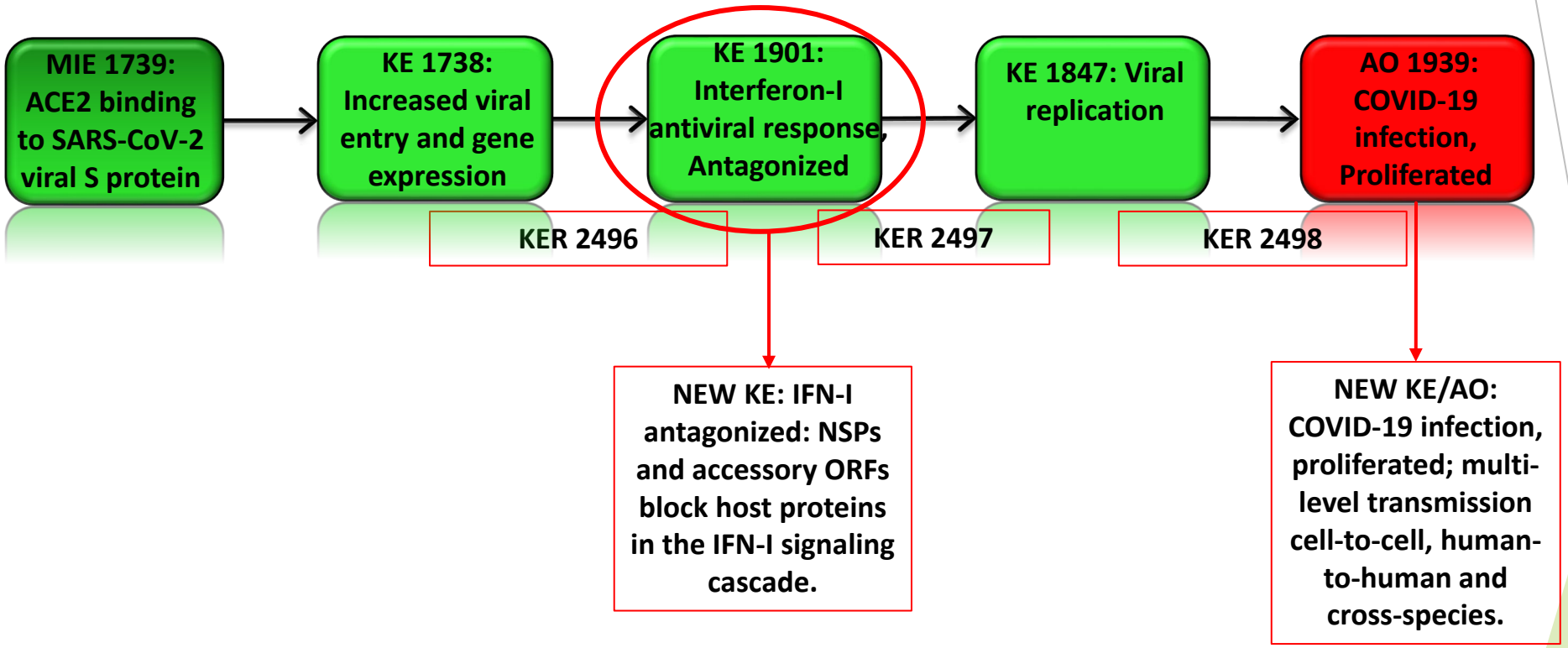
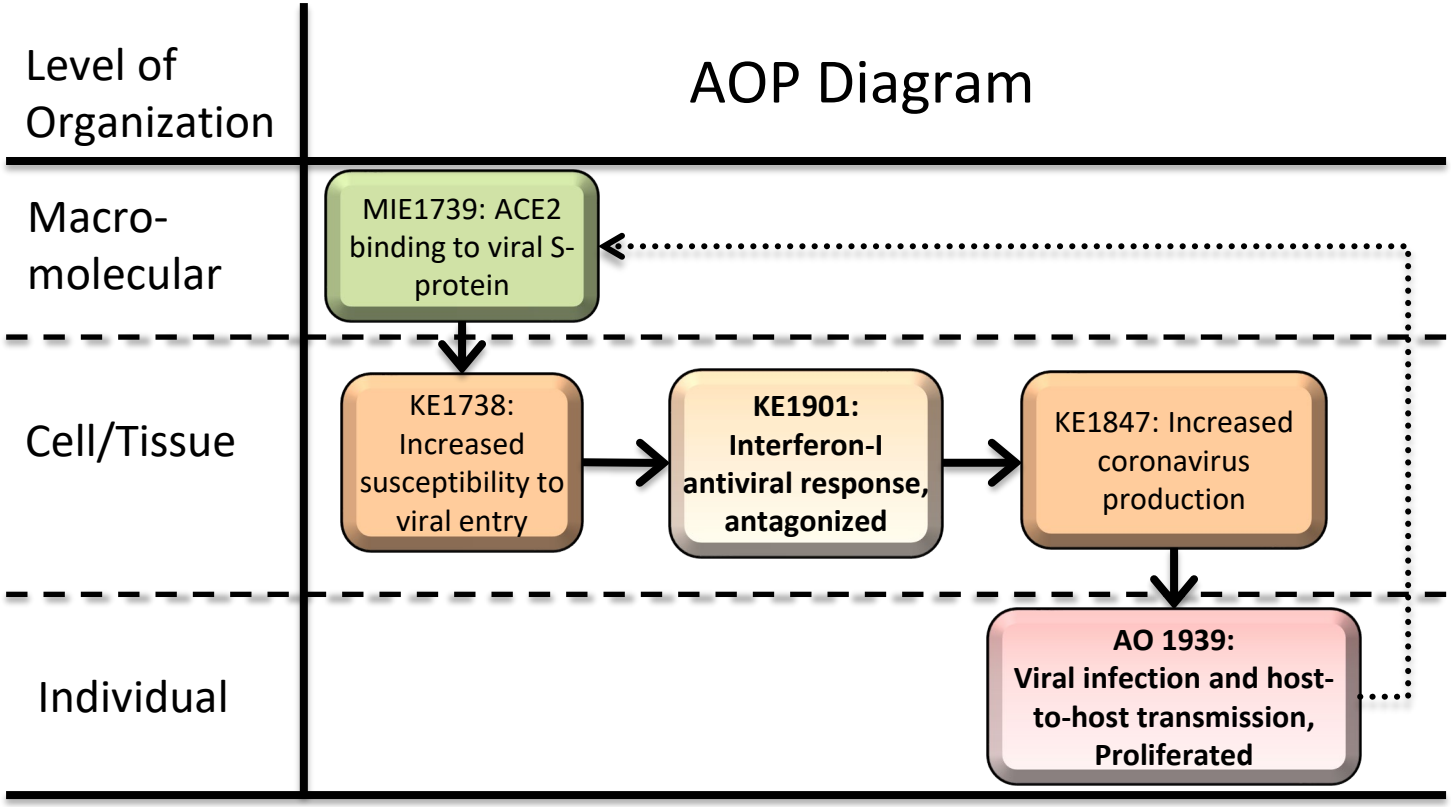
CIAO COVID-19 5th Workshop, March 9-10, 2022

AOP 430: Sars-CoV-2 Interferon-I antiviral response antagonism and increased viral production leading to viral infection proliferation



AOP 430: Sars-CoV-2 Interferon-I antiviral response antagonism and increased viral production leading to viral infection proliferation



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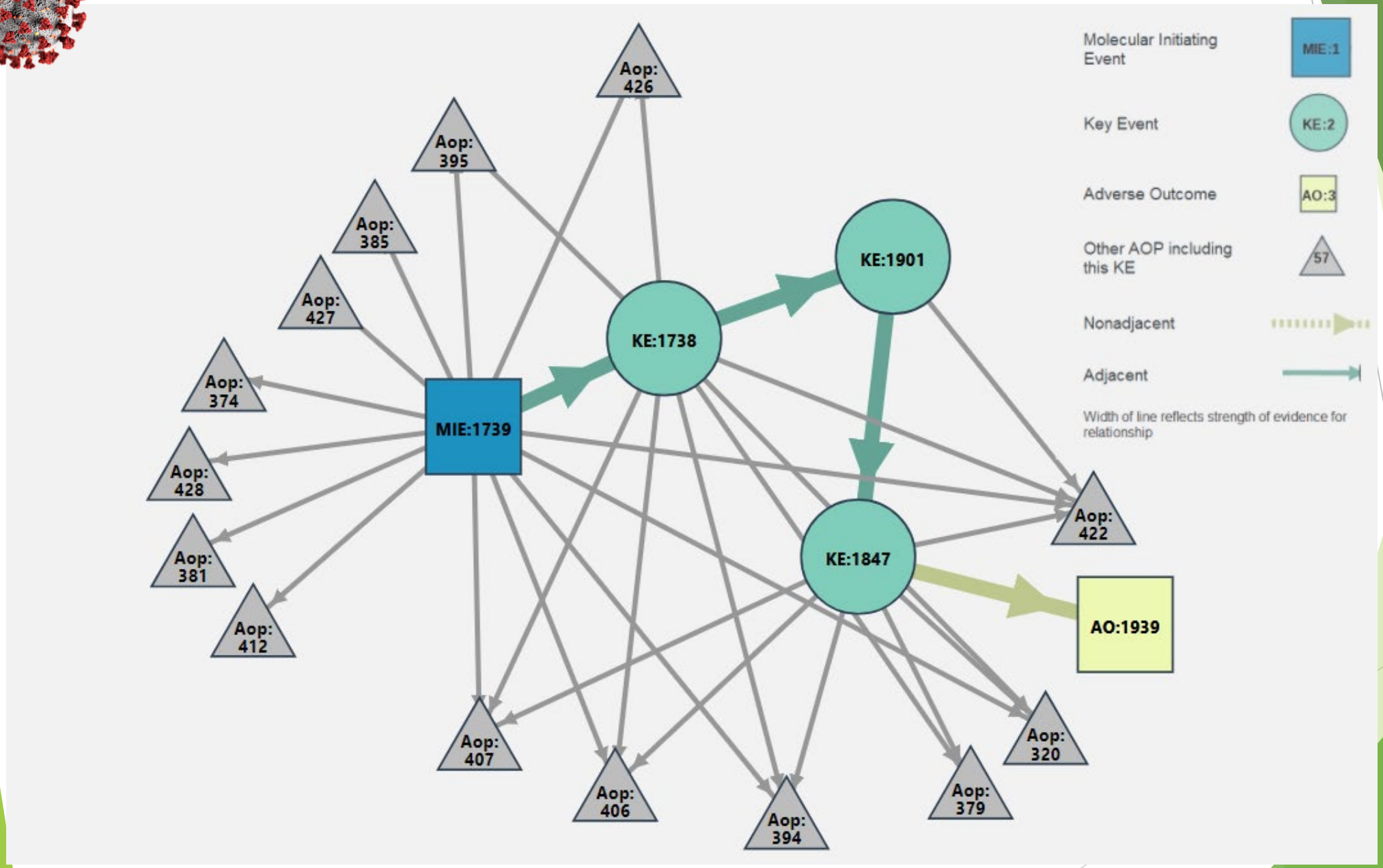
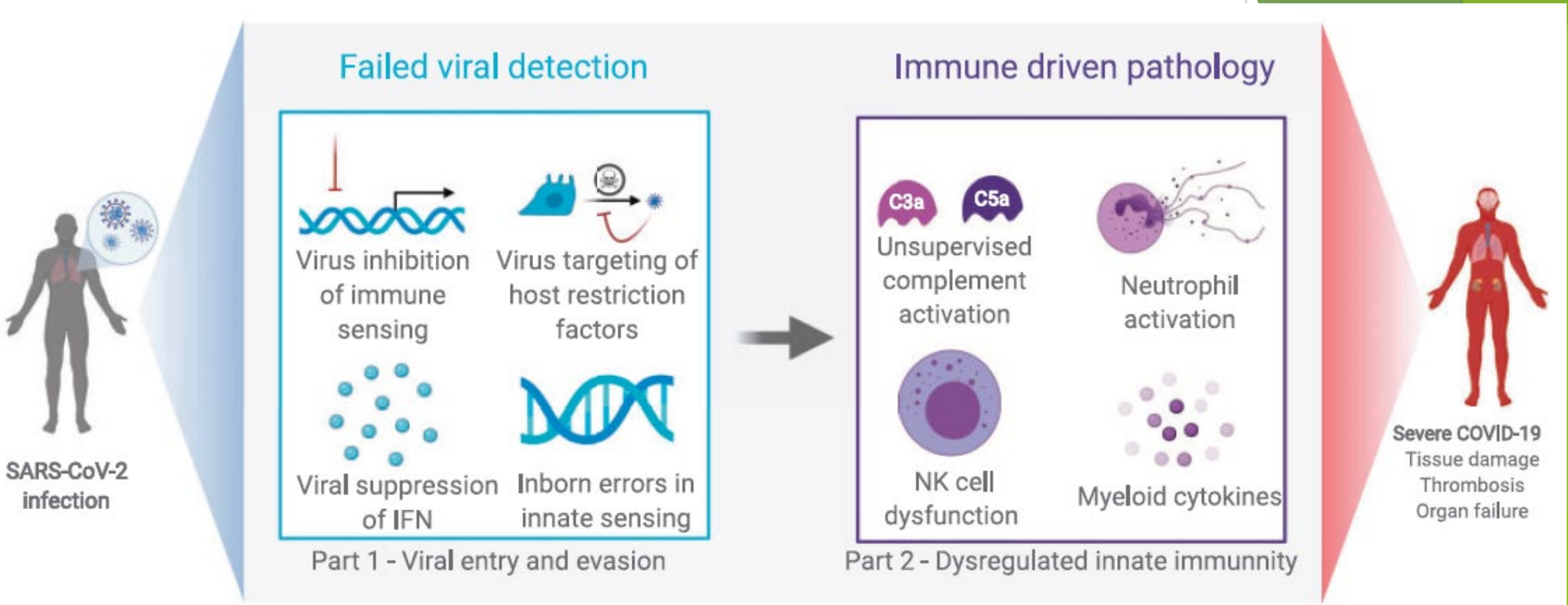
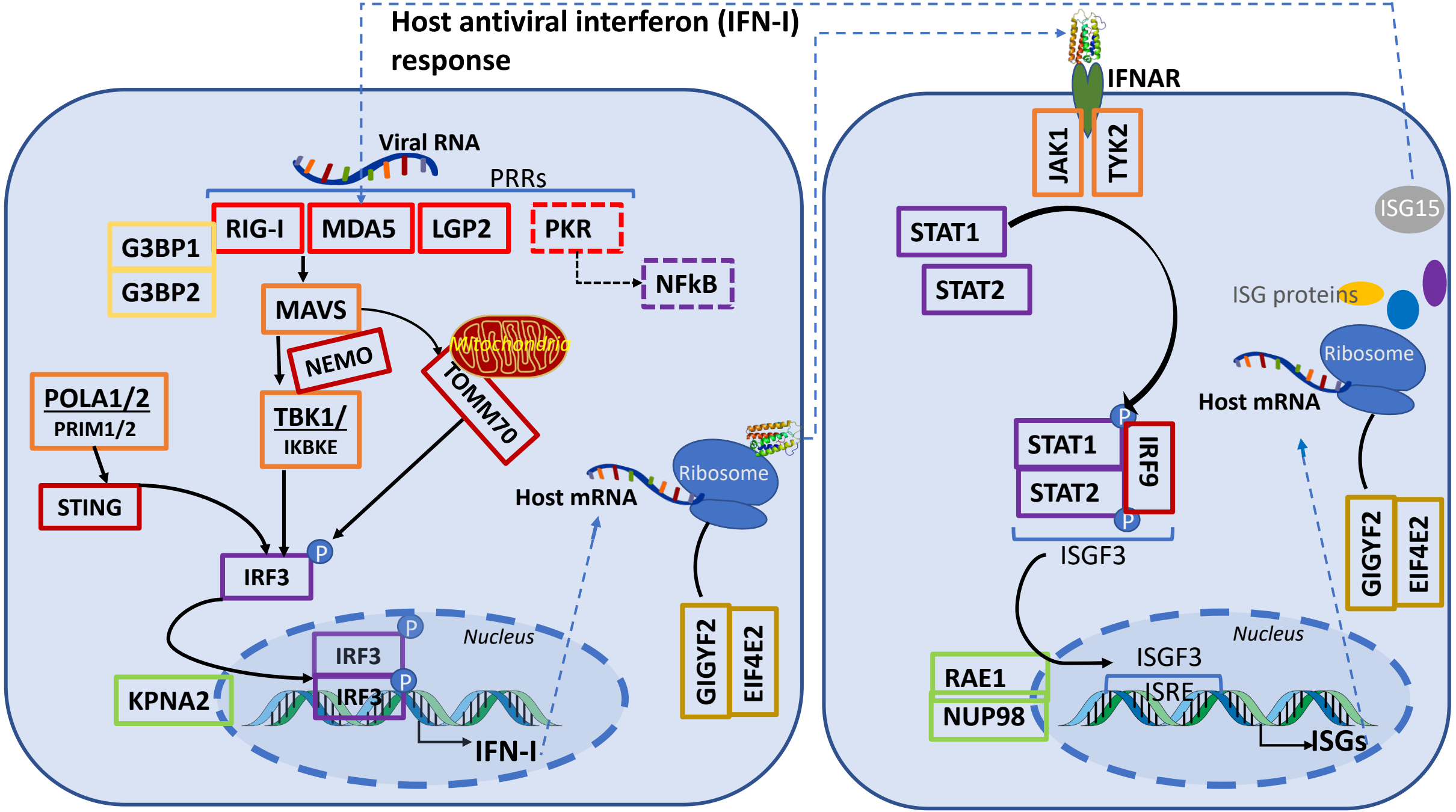
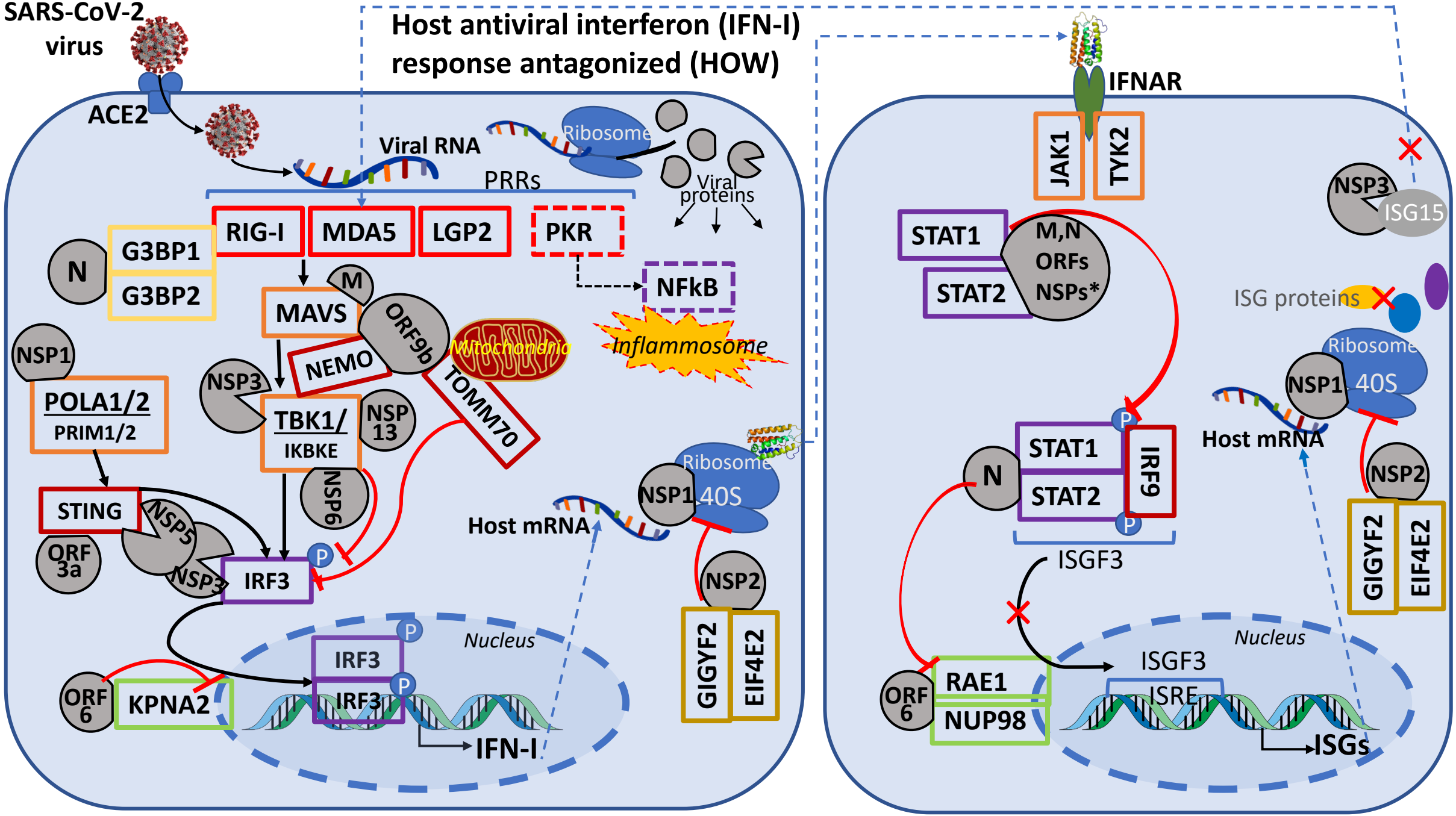
AOP 430 network view

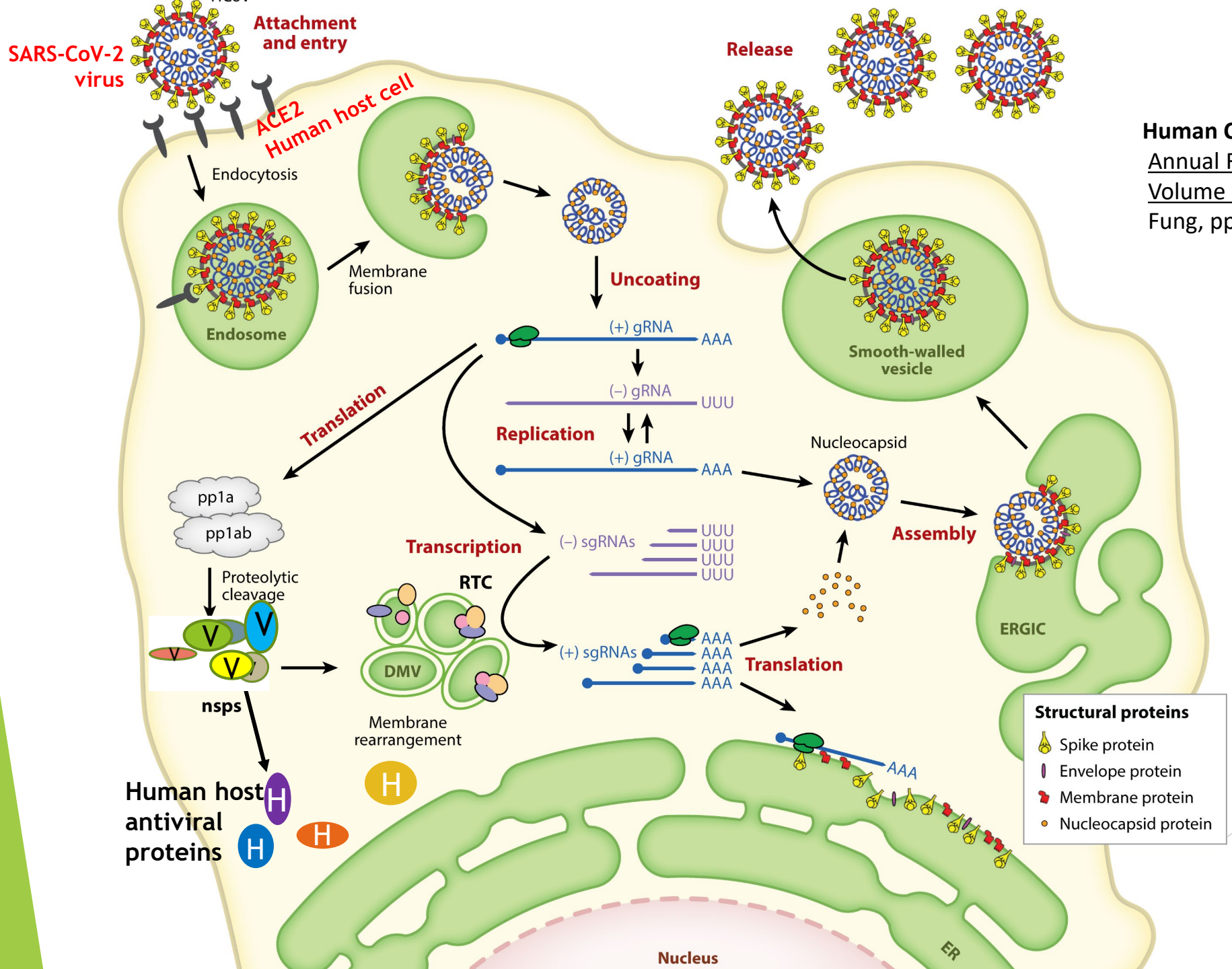




Innate immunology in COVID-19—a living review.
Part I: viral entry, sensing and evasion
Coveney et al. 2020 doi:
10.1093/oxfimm/iqaa004





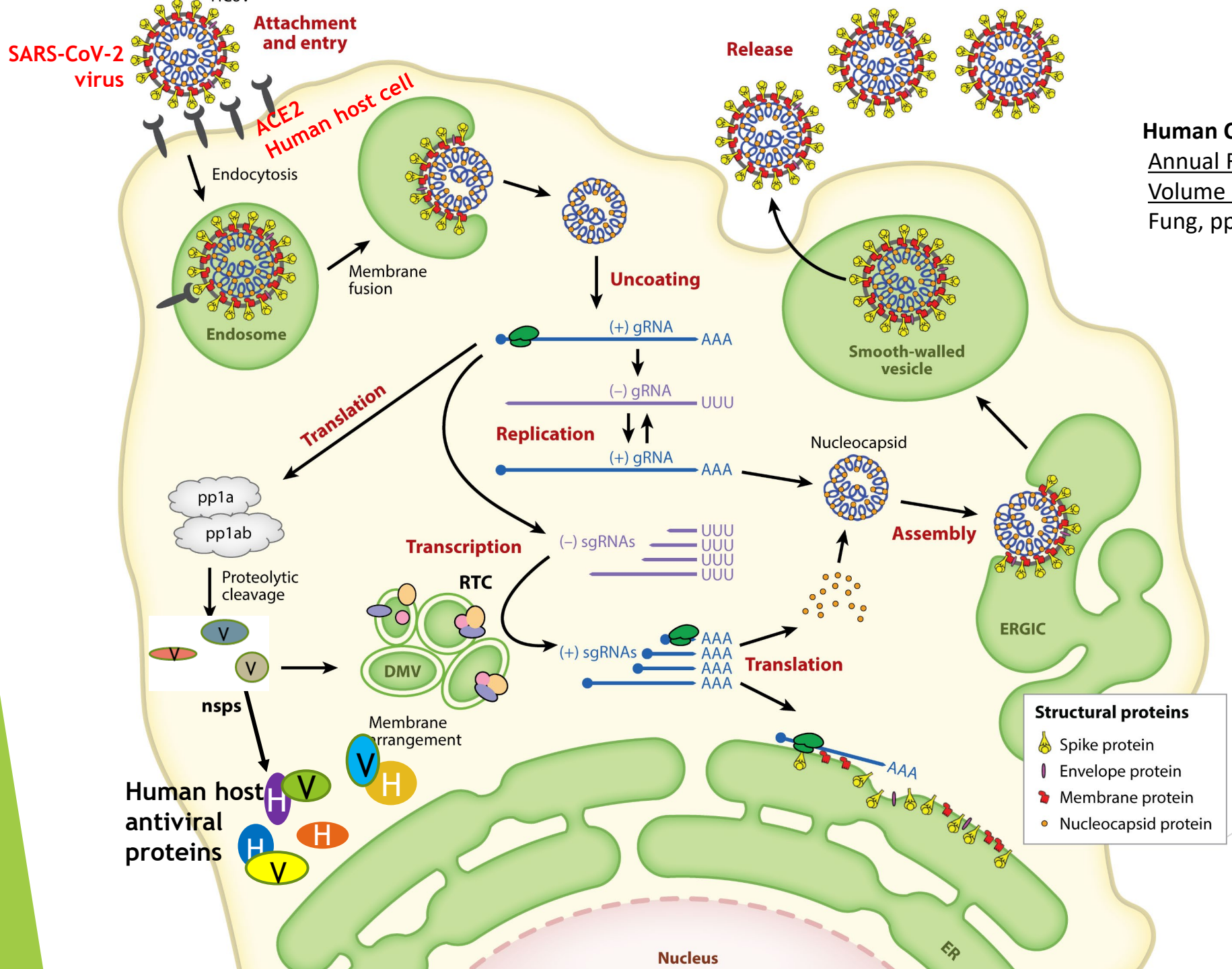


Human Coronavirus: Host-Pathogen Interaction

Annual Review of Microbiology

Volume 73, 2019

Fung, pp 529-557



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Essentiality of IFN anti-viral response antagonism to downstream events

- ACE2 and TMPRSS2 proteins allow viral entry but are not the only determinant of viral replication
- IFNs are a key determinant in the progression of COVID-19.
  - Entry is essential for viral transcription→IFN antagonism→viral replication: viral load→disease/inflammatory responses and/or transmission.
  - Virus replication is prevalent in nasal, upper airway/lung, and enteric tissues that provide paths to distal organs and out of the body (to environmental exposure routes).

KER 2496: Increased susceptibility to viral entry (KE1738) *leads to* IFN-I response, antagonized.

↓

KE 1901: IFN-I response, antagonized

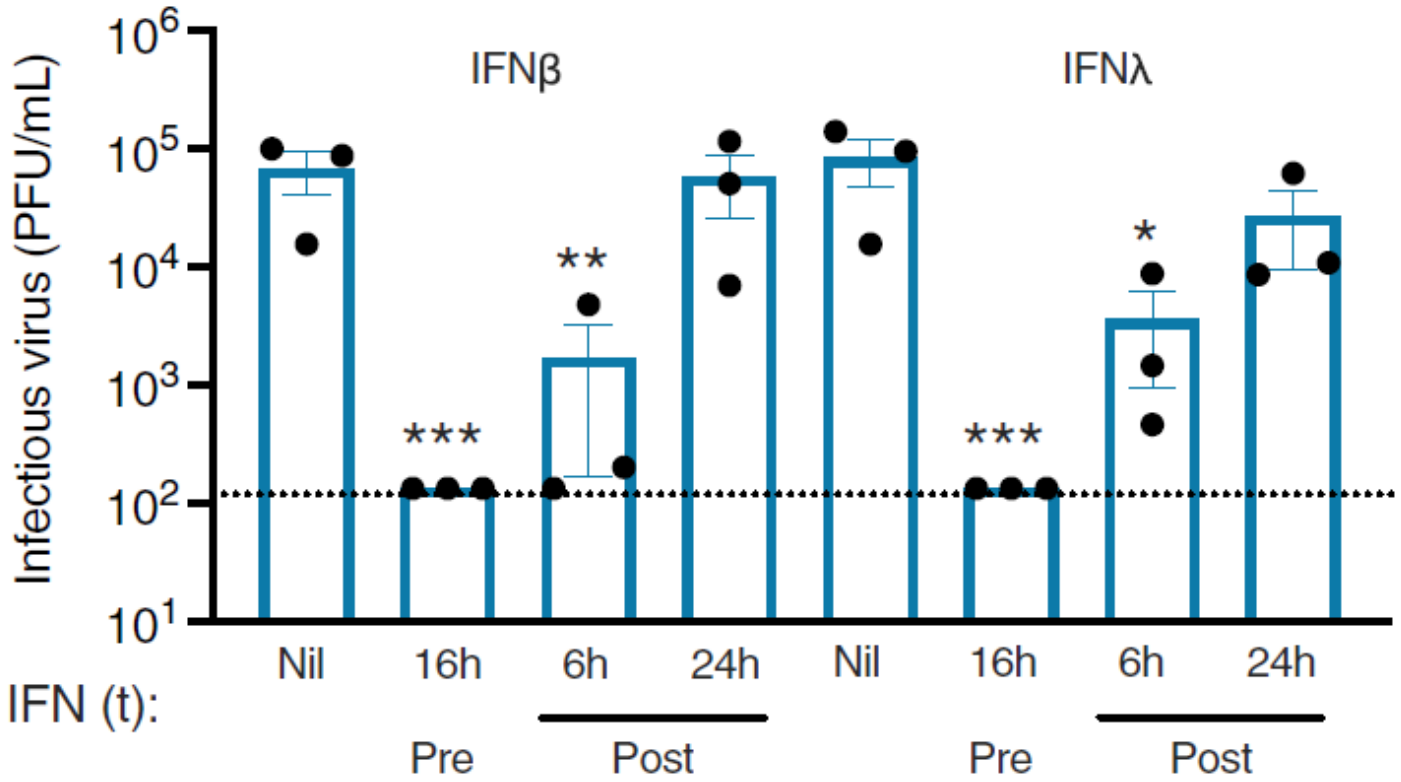
↓

KER 2497: IFN-I response, antagonized leads to Increased SARS-CoV-2 production (KE1847).

- Biological plausibility
- Empirical evidence
  - Temporal concordance
  - Upstream: Dose/measured state
  - Downstream: Predicted/measurable response
- Uncertainties

IFN and Increased SARS-CoV-2 production Biological plausibility

- Interferon administered upon exposure abrogates viral production (Lopez, Madonov, Hatton, Hoaglund)
- IFN autoantibodies in some patients are an underlying factor for more severe disease (Bastard, Busnadiego)



Exogenous IFN-I/III treatment controls SARS-CoV-2 replication. Nasal ALI cultures were either pre-treated (Pre) with IFNβ (1000 IU/mL or IFNλ1 100 ng/mL, for 16 h prior to infection with SARS-CoV-2, or IFN treatment was applied at 6 or 24 hpi (Post). Plaque assay on apical washes collected at 48 hpi. Dotted line indicates lower limit of assay detection.

Hatton et al. 2021 NATURE COMMUNICATIONS 12:7092
https://doi.org/10.1038/s41467-021-27318-0

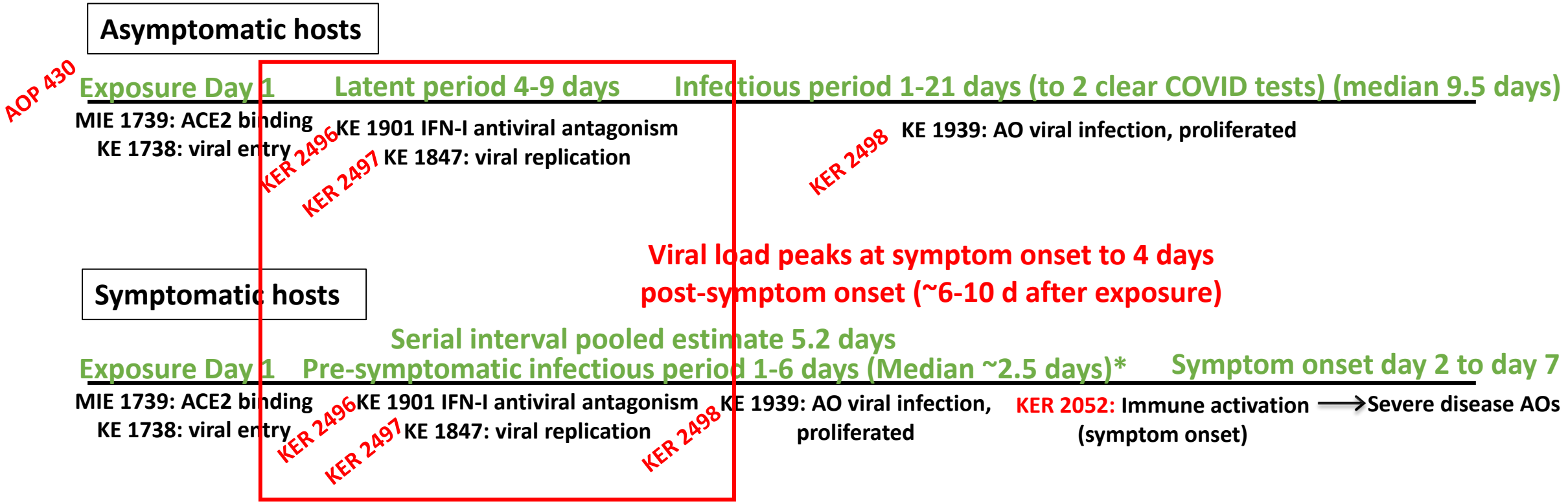
IFN and Increased SARS-CoV-2 production Empirical evidence

- Empirical support for temporal concordance
  - Interferon expression delayed by SARS-CoV-2 vs. other viruses (Galani, Channappanavar)
  - Untuned/imbalanced response in moderate-to-severe cases (Galani, Blanco-Melo, Hadjaj, Hatton, Rouchka)
- IFN antagonism and viral replication/production may occur simultaneously but in separate cellular compartments
  - KE 1847 production is downstream based on essentiality:

    →if IFN is not antagonized (IFN↑), viral production↓ (reduced/eliminated)

    → IFN↓, viral load↑

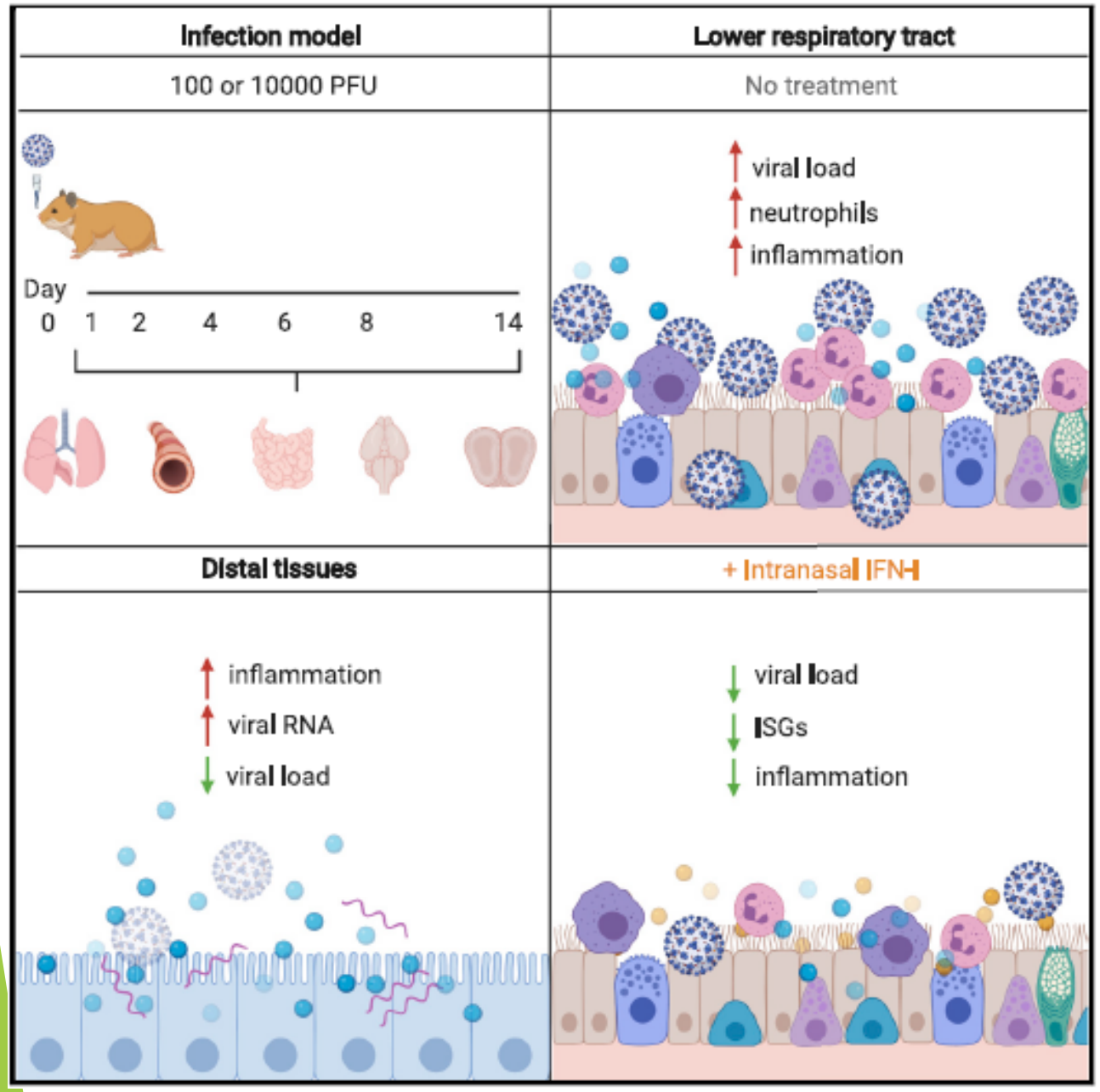
COVID-19 disease infectious period early stage timelines



Serial interval: the time interval between the onset of symptoms in the primary and secondary case.

Latent period: period from exposure to infectiousness.

Serial interval 5.2 days – 2.5 days pre-symptom infectious period ≈ 2.7 days Latent period



Hoaglund et al. 2021

Leveraging the antiviral type I interferon system as a first line of defense against SARS-CoV-2 pathogenicity

Immunity 54, 557–570

doi.org/10.1016/j.immuni.2021.01.017

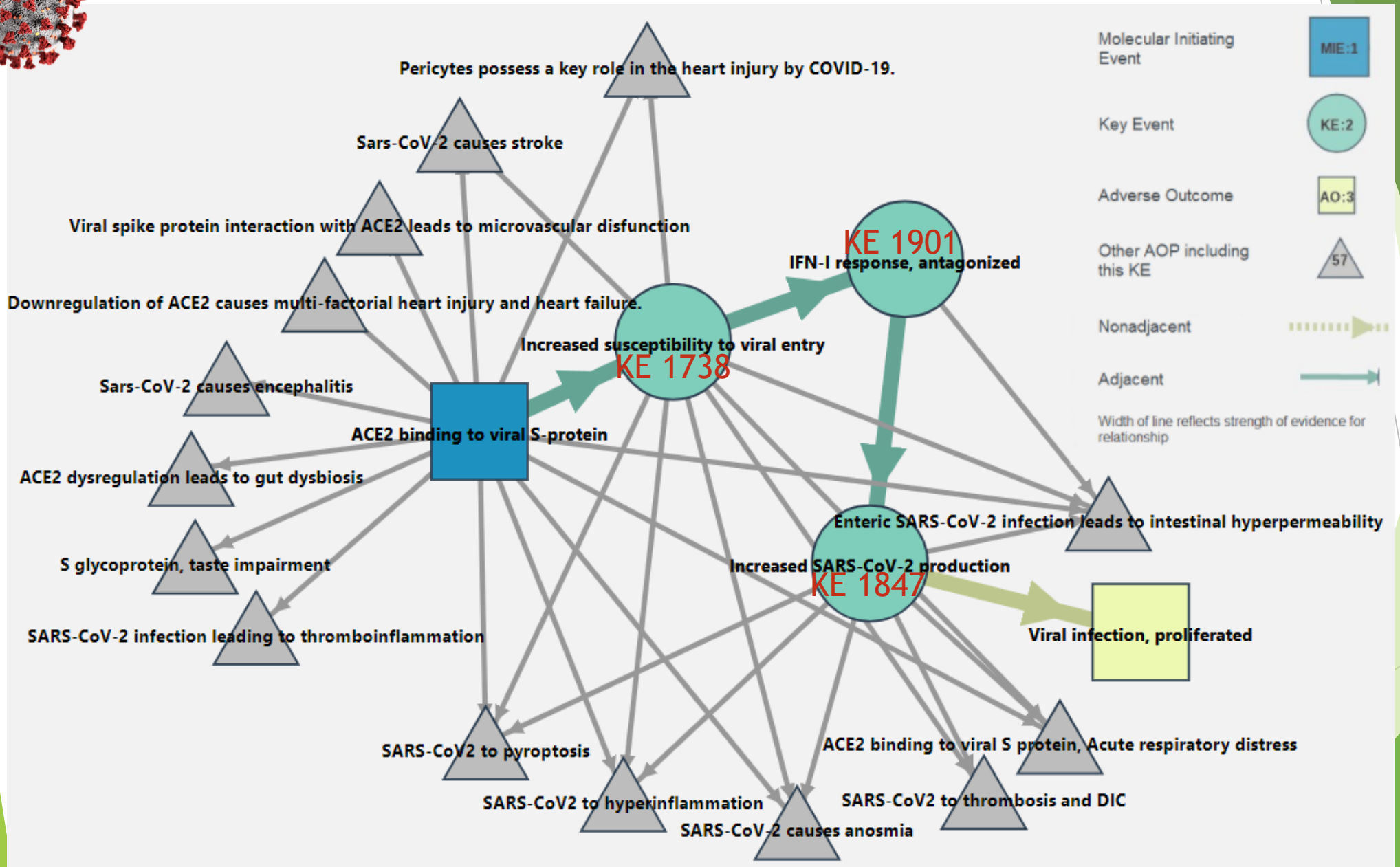
Highlights

- Infection and transmission can be initiated by respiratory or ocular exposure
- Systemic inflammation occurs despite little productive replication in distal tissues
- Intranasal IFN-I administered pre- or post-virus challenge reduces disease burden

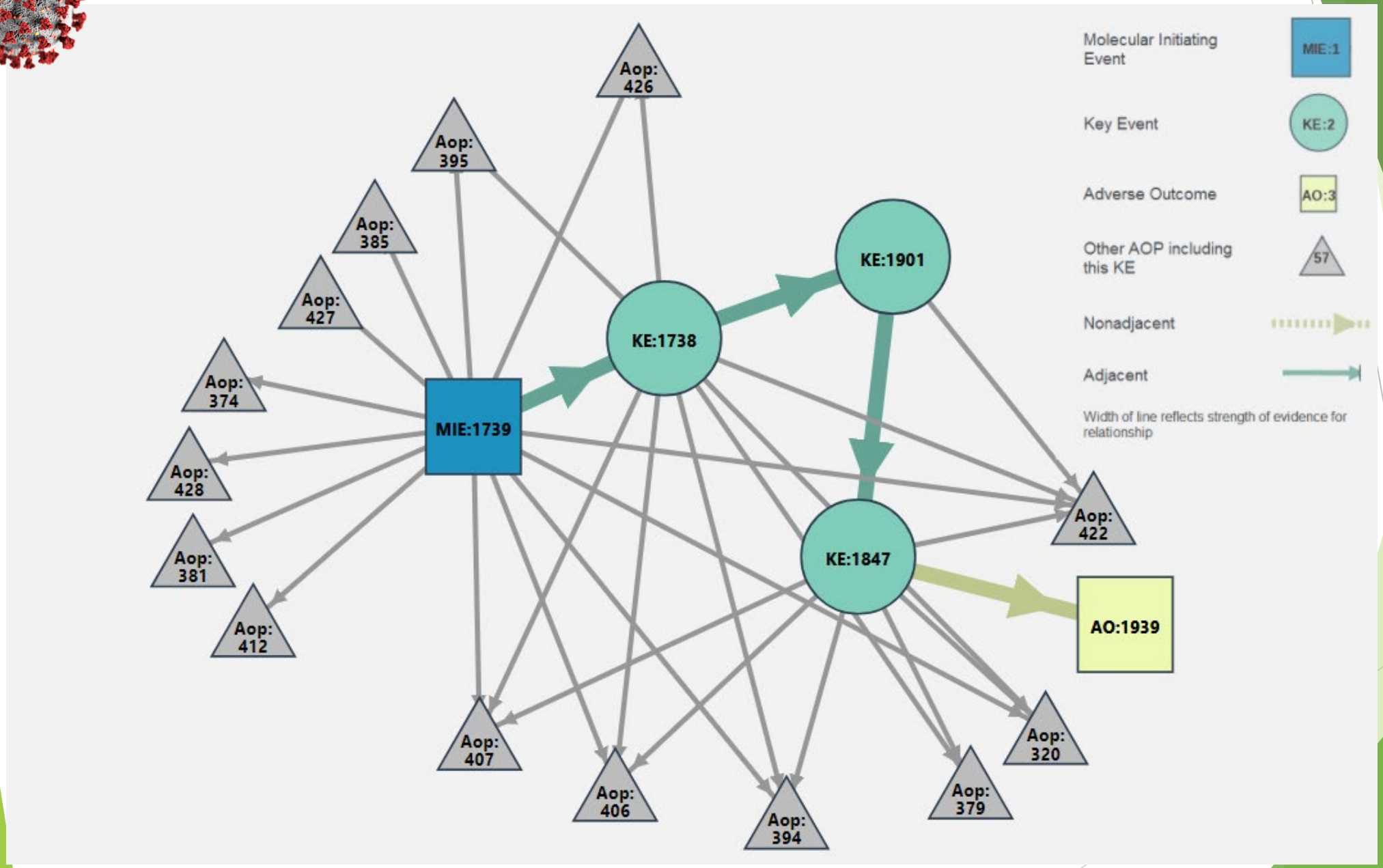
IFN and Increased SARS-CoV-2 production Cell and Tissue type specificity

- Tissues
  - Intestine – Stanifer, Lamer
  - Nasal – Hatton, Ahn
  - Lung – Broggi
  - Upper airway - Mick

AOP 430 network view



AOP 430 network view



AOPs using MIE 1739, ACE2 binding to viral S-protein

Currently include KE 1738→KE 1847

- Viral replication required for downstream events:
- AOP 320
- AOP 379
- AOP 394
- AOP 406
- AOP 407
- AOP 422
- AOP 430: KE1738-KE1901-KE1847

Directly leading to adverse KE?

- No viral replication required?
- AOP 374 ? Brain cells neuroinflamation
- AOP 381 ACE2 downregulation
- AOP 385 ACE2 dysregulation
- AOP 395 ? Pericytes 1738→BBB disruption
- AOP 412 ACE2 inhibition
- AOP 426 ? Heart failure→1738
- AOP 427 ACE2 downregulation
- AOP 428 ACE2 dysregulation

IFN and Increased SARS-CoV-2 production Discussion points

- Uncertainties: differing disease outcomes reported for interferon up- or downregulation and associated timing; different interferons
- Dosage: Initial vs. post-produced load
- Point of departure: Is KE after MIE 1739 (ACE2 binding to Spike protein) dose-dependent? Is replication required for ACE2 dysregulation?
- MIE 1739 as starting point? AOP 430 as “hub COVID MIE” module?
- Rules of AOP framework – SARS-CoV-2 stressor or agnostic?